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Response to EPA for P-17-0294
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Executive Summary

The U.S. EPA has identified the peroxide PMN chemical (P-17-0294)(CAS# 182893-11-4) as a potential respiratory sensitizer based on one older skin sensitization study in guinea pigs that is only marginally positive. EPA also has a marginal concern for the PMN substance as a mutagen and an oncogen.

Regarding respiratory sensitization, there is not yet an accepted and validated method to test or predict whether a specific substance will cause respiratory sensitization (Holsapple, 2005; Arts, 2007). Substances that are recognized human respiratory sensitizing agents have been identified as such only through the use of established clinical (medical) criteria (Cochrane, 2015).

With respect to the relationship between skin sensitization and respiratory sensitization, the European Union technical staff has concluded, “it is important to note that in reality only a very few precedents for the elicitation of pulmonary reactions by skin sensitizing chemicals in humans have been observed, and in practice it may not represent a significant health issue” (ECHA, 2015).

In summary, we conclude there are no test data, scientific literature references, clinical testing, or occupational exposure records for the PMN substance or on structural peroxide analogs that would warrant the EPA concern. In addition, there do not appear to be any QSAR analyses available that would indicate the PMN substance is a respiratory sensitizer: there are no known data showing peroxides have caused respiratory sensitization that can be used in the training sets to develop such QSAR tools. And it should be stressed that existing sensitization QSAR model structural alerts not only do not include the peroxy functional group, but are based on chemical sensitizers, not specifically chemical respiratory sensitizers/asthmagens (ECHA, 2015).

We do not understand why EPA has recommended that self-contained breathing protection be used in the workplace. Existing engineering controls and PPE have been shown to provide adequate protection during 12 years of production and use of the PMN chemical in Europe and a similar, effective approach will be used in the U.S.

Therefore, we have concluded that: (1) there are no data on the PMN chemical that indicate it should be considered a respiratory sensitizer; (2) historical manufacture and use of peroxides for more than 30 years in the United States has not resulted in respiratory sensitization concerns by U.S. government agencies; (3) worker health assessment does not indicate a respiratory sensitization issue exists for peroxides; (4) existing engineering controls and PPE ensure that workers will not be exposed to hazardous amounts of the PMN substance; (5) we do not know what EPA's definition of respiratory sensitizer is; (6) the sensitization process in skin is different from that in the respiratory system; (7) a classification of respiratory sensitization should not be based on the results of one animal laboratory sensitization skin study; (8) the results of the one, older skin sensitization study on the PMN chemical are only marginally positive; (9) a technically-based Weight-of-Evidence (WoE) approach for respiratory sensitization is appropriate for the PMN chemical; and (10) based on previously submitted peroxide studies EPA should not have a concern for oncogenicity of the PMN substance.

Detailed comments and questions

Our detailed comments that support these conclusions are provided below, as well as a number of key questions for EPA staff.

(1) <u>There are no data on the PMN chemical that indicate it should be considered a respiratory sensitizer</u>

We have conducted an exhaustive literature search of global databases and the results indicate that there are no data on the PMN chemical that would in any way indicate that it is a respiratory sensitizer. Our search strategy is provided in ATTACHMENT 1.

<u>QUESTION</u>: does the EPA have any published or unpublished data on the PMN substance or structural analogs that would indicate the PMN substance is a respiratory sensitizer?

(2) <u>Historical manufacture and use of peroxides has not resulted in respiratory sensitization concerns by U.S. government agencies</u>

Peroxides have been safely used in U.S. industry for over 30 years and a number of peroxides have been added to the TSCA Inventory since 1976 through the PMN process. For example, methyl ethyl ketone peroxide (MEKP), a ketone peroxide similar in chemical structure to the PMN substance, has been estimated to have had a 1979 production in the U.S. of 4.09×10^5 kg and 2.68×10^6 kg production in 1974 (SRI, 1989). An estimated

20,000 workers may have been exposed to MEKP in 1974 (NOHS, 1974). One of the documented uses of MEKP since at least the 1980's has been in the production of fiber-glass reinforced polyester resin hulls for boats where workers spray the hulls with polyester resins containing free styrene monomer and MEKP (Brigham, 1985; NIOSH 1988).

To our knowledge, none of the peroxides used in U.S. industry have been classified as respiratory sensitizers by EPA. Neither the U.S. NIOSH nor the U.S. OSHA defines or regulates any peroxide as a respiratory sensitizer from an occupational exposure standpoint. The U.S. FDA does not define or regulate peroxides as respiratory sensitizers. And to our knowledge the U.S. CPSC does not define or regulate any peroxide as a respiratory sensitizer.

In reviewing OSHA Annotated Tables Z-1, Z-2, and Z-3, only two peroxides appear: benzoyl peroxide and hydrogen peroxide, both for irritation effects, neither indicated as respiratory sensitizers, and both used safely for many years in the workplace and even currently in consumer products, such as over the counter drug products (benzoyl peroxide), without reports of respiratory sensitization as far as we are aware.

A review of the current <u>NIOSH *Pocket Guide to Chemical Hazards*</u> *that contains 677 chemical entries* for which the National Institute for Occupational Safety and Health (NIOSH) has set recommended exposure limits (RELs) reveals that NIOSH includes only three peroxides in the list: (1) benzoyl peroxide, for severe irritation and sensitization dermatitis possible, (2) methyl ethyl ketone peroxide for severe irritation, etc. possible, and (3) hydrogen peroxide for severe irritation possible. NIOSH has not identified respiratory sensitization as a health hazard for any peroxide.

In addition, certain peroxides, including the ketone peroxide MEKP, have been approved for many years by the U.S. FDA for industrial use in the production of plastic food contact containers. The U.S. FDA to our knowledge has never concluded that peroxides in these FFDCA-regulated applications, which are very similar in principle to industrial applications for peroxides that employ high temperatures for example during the production of plastic food contact containers, are respiratory sensitizers.

A number of software tools (OECD Toolbox, Derek, etc.) are available that include modules to predict respiratory sensitization. The manufacturers of these systems collect information from the peer-reviewed literature to identify those chemicals that have been linked to *respiratory sensitization in humans*. However, none of these systems have any respiratory sensitization data on peroxides. For example, the OECD Toolbox Profiler (Version 1.1, April, 2017) for respiratory sensitization includes the following structural alerts within the Profiler:

Diisocyanates
Anhydrides
Lactams
Acyl chlorides
Phenyl acetates
N-acetoxyalkylmaleimides
Dialkyl phenylthiophosphates
Benzhydrazides
Cyanoacrylates
Acrylates
Methacrylates
Indgotine and related
4-Methylenecyclohexa-2,5-dien-1-imines
Azocarbonamides
Hydroquinones
Phenylenediamines
Aminophenols
4-Allyphenols
4-Hydroxymethylphenols
Di-aldehydes
Formaldehyde
Thioureas
Ethanolamines
Ethylenediamines
Dichloroacetamides
Piperazine
Hexamine
Ninhydrin and related
Fufuryl alcohol
Epoxides
Thiols
Benzisothiazolin-3-ones
N-alkylthiosuccinamides
Activated sp3 carbon w/+charged leaving group
Chloro nitrogen
Vinyl benzene
N-phenylacetamides
Aryl hydroazines
2-Chloro-1,5-dinitro-3-(trifluormethyl)benzols
Tetrachloroisophthalonitrile
Bis-1,2,4-trichlorobenzenes

As can be seen, none of the listed structural alerts is relevant to peroxides.

As a part of the overall TSCA PMN review process, EPA groups PMN chemicals with shared chemical and toxicological properties into Chemical Categories in order to streamline the process for Agency review of new chemical substances. For many years, perhaps since the late 1970's or 1980's, the Agency has included the category of peroxides in its Chemical Categories list, and the current listing describes aquatic toxicity as the only key EPA concern from a new chemicals standpoint (USEPA, 2010). The EPA Chemical Categories listing for peroxides does not conclude that they may be respiratory sensitizers.

Therefore we do not understand why the Agency, to our knowledge for the first time since TSCA was enacted in 1976, is concluding that a peroxide, the PMN peroxide, may be a respiratory sensitizer whose use in 2017 may represent an unreasonable risk. There are no new occupational health data or toxicology studies known to us that in any way link the new peroxide to respiratory sensitization in humans. It is surprising therefore that EPA is proposing to classify the PMN peroxide as a respiratory sensitization without any data or weight of evidence (WoE) approach. If there is no clear link to this hazard we do not understand how EPA concluded that there is an unreasonable risk under TSCA.

***<u>QUESTION</u>*: Does the Agency have specific new human data that have led it to draw the conclusion that the new peroxide is a respiratory sensitizer? If so, we would like to review the specific new information (e.g., new human data, the results of QSAR modeling, etc.).**

(3) <u>Worker health assessment does not indicate a respiratory sensitization issue exists for peroxides</u>

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<u>*QUESTION*</u>*: does the EPA have specific human exposure concerns regarding the new peroxide that would support a conclusion of unreasonable risk?*

(4) <u>Existing engineering controls and PPE ensure that workers will not be exposed to hazardous amounts of the PMN substance</u>

We do not understand the EPA required use (and confirmation of use by customers) of a positive pressure facemask (APF 1000) with respect to the PMN chemical. The use of such significant PPE should be reserved for working conditions that present a high hazard and risk level based on recognized human health concerns. To our opinion, there is no scientific basis for the selection of such PPE in this case, and in addition U.S. customers will have large laminar air flow exhaust hoods, where the primary purpose is to control styrene exposure levels, but are also expected to capture all airborne vapors including peroxide vapors.

Human respiratory sensitization concerns exist for the chemical category diisocyanates (USEPA, 2010). In its current TSCA New Chemicals Program (NCP) Chemical Categories document, EPA states what it considers sufficient for worker protection, as follows:

> "Engineering controls should serve as the first, most effective means of reducing airborne concentrations; as appropriate an NIOSH/MSHA-approved respirator should be used as a secondary tool to lower exposure."

If this approach is sufficient for new diisocyanates, it certainly should be adequate in the case of the PMN chemical, and we agree to follow these recommendations for the PMN chemical.

Please note that the current suggested respiratory protection for the PMN substance as noted on our SDS in the case of vapor or aerosol formation is to use a respirator with an approved organic vapor cartridge. The use of organic vapor cartridges is specifically recommended by the 3M Company for methyl ethyl ketone peroxide (MEKP), a ketone peroxide similar to the PMN substance in chemical structure (3M, 2015).

There is no OSHA PEL for MEKP, however a ceiling limit of 0.2 ppm (1.5 mg/m3) has been set as an REL by NIOSH, a TLV by ACGIH and as a PEL by CAL/OSHA (US Dept. of Labor, 2015). Our European site that manufactures MEKP and the PMN substance confirm that organic respirator cartridges are used and that no reports of respiratory asthma in workers are known. Further, industrial hygiene monitoring at our European site for MEKP showed an airborne level of less than 1 mg/m3. In addition, filling machines are placed in completely enclosed cabinets with local exhaust ventilation; therefore no exposure of worker during filling operations is expected.

The 3M Company recommends the use of a full face piece respirator with an organic vapor cartridge for methyl ethyl ketone peroxide and this is what we currently use for MEKP, and what we plan to use for the PMN ketone peroxide. In its 2015 Respirator Selection Guide 3M states the recommended cartridge can be used at 10 times the OEL to protect workers. Therefore we consider it is reasonable that this same type of organic vapor cartridge will also be effective for the ketone peroxide PMN substance.

<u>QUESTION</u>*: *does EPA agree that workers will be protected if they follow the guidelines that EPA has published for new diisocyanates, and specifically use the 3M-recommended full face piece respirator with organic vapor cartridge specifically recommended by 3M for MEKP?

(5) We do not know what EPA's definition of respiratory sensitizer is

The definition of a respiratory sensitizer is the critical starting point from which any hazard assessment for this endpoint should begin. It has been generally accepted that for a chemical to induce an allergic sensitization reaction a hyper-responsive immunological mechanism is involved with an exogenous low molecular weight chemical resulting in symptoms such as allergic asthma and rhinitis (Cochrane, 2015; Basketter, 2017). In the example of allergic respiratory sensitization, this means that the induction of asthma symptoms such as airway hypersensitivity is a result of direct activation of the immune system after more than one exposure to the chemical.

Many chemical substances are irritants and cause redness, swelling and physical damage to the skin, the eyes, and mucous membranes of the nose and respiratory tract, etc. after one exposure: damage to the respiratory tract can be triggered by nonspecific irritation (Holsapple, 2005). As opposed to respiratory sensitization, there is generally no latency period associated with irritant-induced respiratory system effects (Vincent, 2017). These types of irritant responses should not be considered allergic sensitization reactions.

***QUESTION*: What is the U.S. EPA definition of a respiratory sensitizer? Has this definition been accepted throughout EPA? Has EPA communicated its definition to the public and regulated community?**

(6) The sensitization process in skin is different from that in the respiratory system

Not all chemicals that induce a specific immune response will have the potential to cause respiratory sensitization (Boverhof, 2008). In fact, a larger number of compounds are associated with skin sensitization and are believed to have no sensitizing effect on the respiratory system (Kimber, 2005). And conversely, a substance such as phthalic anhydride that is a respiratory sensitizer in humans does not appear to have a potential to cause skin sensitization (Basketter, 2017).

In humans, skin sensitization is only rarely associated with chemicals that are known to be respiratory sensitizers (Isola, 2008). This follows because the mechanism of skin sensitization is different from the mechanism for respiratory sensitization.
All known respiratory sensitizers tested, have tested positive in animal skin sensitization tests, however, less than 1% of skin sensitizers are also respiratory sensitizers (Basketter, 2016; Dearman, 2013). When reviewing the common classes of chemicals

associated with respiratory sensitization in humans (Lalko, 2012; Isola, 2008), peroxides as a category are not included on any known published list.

Skin and respiratory sensitizers both stimulate T cells; however, their respective pathways that lead to the development of an allergic response are very different (Basketter, 2017). Differential activation of subpopulations of T helper (Th) cells, (i.e. Th1 and Th2) cells will determine which type of sensitization occurs: skin or respiratory. The specific characteristic of chemical respiratory allergens is their ability to induce the development of T helper 2-type immune responses (Kimber, 2005; ECHA 2015). Respiratory sensitization has been associated with preferential induction of the Th2 (T2 helper) cells which have high amounts of interleukins (IL-4, 10 and 13 (Boverhof, 2008; Hamelmann, 1999; DeJong, 2009)). Skin sensitization is associated with the production of Th1 (T1 helper) cells (Basketter, 2017; ECHA, 2015).

Actually, the two types of T helper cells and their cellular products (cytokines) antagonize the proliferation of the other cell population: this is an important distinction from a hazard assessment and a regulatory perspective (Boverhoff, 2008). There are no data showing any effects on IgE or IL-4, 10 or 13 levels for the PMN substance, or structural analogs that would lead EPA to consider it a respiratory sensitizer.

For example, trimellitic anhydride (TMA) and 2,4-dintrochlorobenzene (DNCB) exhibit a clear positive result for contact sensitization in mice, but only TMA, not DNCB, is known to cause occupational respiratory allergy in humans (Dearman, 1992). Exposure in mice to TMA results in an IgE antibody response, but not to DNCB. Topical exposure in mice to both chemicals resulted in delayed (24 hour) hypersensitivity, but in addition TMA induced an immediate (1 hour) dermal reaction, suggesting an effect by hapten-specific IgE. Serum from TMA-treated mice, but not with control mice or DNCB-treated mice, induced immediate hypersensitivity in untreated mice.

On the other hand, phthalic acid is a well-known cause of occupational asthma, but it is not considered a skin sensitizer in humans (Venables, 1989). Respiratory sensitizers typically induce positive responses in animal assays designed to identify skin sensitizers (e.g., guinea pig assays or LLNA assays), but these chemicals fail to cause allergic contact dermatitis in humans (Dearman, 2012).

Further, isocyanates are recognized respiratory asthmagens in humans, however, allergic contact dermatitis (skin sensitization) is rarely reported in workers with isocyanate asthma (Bello, 2007). Therefore even with isocyanates it has been confirmed that skin sensitization is NOT a predictor of respiratory asthma in humans. Actually isocyanates are probably not good model compounds to use when trying to predict human respiratory asthma across chemical classes because, as these authors mention, unlike many chemicals that are confirmed human respiratory sensitizers, isocyanates do not consistently induce an IgE response that can be measured in human asthmatics

Toxicogenomic studies have examined the induction phase of sensitization and have compared skin sensitizers, respiratory sensitizers and non-sensitizing irritants using the LLNA (Adenuga, 2012; Boverhof, 2009). Genomic transcripts were identified that were specific to respiratory sensitizers and different from irritant chemicals and skin sensitizers. These types of genomic data should be useful in a weight of evidence (WoE) approach to differentiate respiratory sensitizers from skin sensitizers as well as irritants (Colin, 2016).
And finally, according the United Nations Globally Harmonized System (GHS) skin and respiratory sensitizers are classified in two different hazard classes that result in different adverse outcomes (Colin, 2016).

***QUESTION*: On what scientific basis is the Agency concluding that the PMN chemical may cause respiratory sensitization because it induces skin sensitization via a different biological mechanism?**

(7) <u>A classification of respiratory sensitization should not be based on the results of one animal laboratory skin sensitization study</u>

Apparently the Agency staff has predicted that the PMN chemical should be considered a respiratory sensitizer based entirely on the results of one marginally positive GPMT skin sensitization study conducted on the PMN chemical. However, the results of one animal study by itself should not be considered predictive of respiratory sensitization. At the present time there is still no accepted, validated method for the prediction of respiratory sensitization (Briatico-Vangosa, 1994; Cochrane, 2015).

Before concluding that a person has experienced respiratory sensitization as a direct result of exposure to a chemical, it must be clear that the person does not have a history of allergies or a pre-existing asthma condition or a hypersensitive respiratory system such as may be seen with a heavy smoker (Arts, 2017).

The Canadian Centre for Occupational Health and Safety (CCOHS) has stated that a conclusion of human respiratory sensitization can only be reached following an evaluation of human data because there are no recognized animal models for this endpoint (CCOHS, 2008). CCOHS has offered several important factors to consider when evaluating potential respiratory sensitization in humans. These include:

- There must be evidence that a substance can cause respiratory sensitization from human experience
- The agent in question must be specifically identified
- A relationship between exposure to the chemical and development of respiratory sensitivity must be demonstrated
- Asthmatic symptoms would include cough, wheezing, shortness of breath, constriction of airways
- Other potential causes of the reaction must be excluded, such as a history of allergies (personal and family) and/or a previously identified history of asthma, including childhood asthma
- Smoking history is considered a possible contributing or causal factor
- Lung function tests show significant reversible or variable airflow obstruction and/or non-specific bronchial hyper responsiveness
- Results from bronchial provocation tests are positive using the specific substance
- The agent is related to chemical families known to produce occupational asthma.

As can been seen from this list, none of the listed evaluation criteria have been applied to the PMN chemical. Based on the absence of any of these findings, the PMN chemical cannot be considered a human respiratory sensitizer.

***QUESTION**: What scientific data have led EPA to conclude the PMN substance is a human respiratory sensitizer based solely on one animal skin sensitization study?*

(8) The one, older skin sensitization study result on the PMN chemical is only marginally positive

It appears that EPA is basing its conclusion on respiratory sensitization on the results of one guinea pig maximization test (GPMT) performed in 1999. It should first be stated that obtaining false positives using the highly sensitive GPMT have been considered more likely due to the requirement for intradermal injections of the test chemical in combination with a powerful adjuvant (Kligman, 1995; Basketter, 2008).

One of the first false positive study results for the GPMT was reported for sulphanilic acid (Basketter, 1992). This chemical was later classified as a non-sensitizing agent by re-testing the chemical in the local lymph node assay (LLNA), but unfortunately the LLNA also falsely reported that the irritant sodium lauryl sulfate was a skin sensitizer (Basketter, 1998). The test results on sulphanilic acid and sodium lauryl sulfate were determined to be false positives based on extensive human exposure to these chemicals that found neither to sensitize humans (Basketter, 2008).

Actually, a positive response even in the LLNA would not indicate that the test substance is a respiratory sensitizer (Isola, 2008). Only a small subset of chemicals testing positive in the LLNA are known to be respiratory sensitizers.
While the skin sensitization report on the PMN substance concluded it is a skin sensitizer, closer evaluation of the data does not support the conclusion of a clear skin sensitization effect but rather more of an irritant effect, i.e. the same endpoints of skin scaliness and erythema were observed in the rabbit dermal irritation study using the PMN chemical (NOTOX Project 338682).

In the rabbit dermal irritation study, all test animals showed maximum scores for erythema (skin redness), and all test animals showed skin scaliness 14 days after the initial exposure. The skin sensitization study also reported the same erythema and skin scaliness in the test animals, very similar to the test animals in the skin irritation study. The PMN chemical is a severe skin irritant and therefore skin effects in animal studies are expected.

In the skin sensitization study on the PMN substance (NOTOX project 338704), the peroxide was injected into the skin during preliminary testing: concentrations as low as 2% induced necrosis (cell death) in all animals. In the intradermal injection phase of the main study, all animals showed erythema and signs of necrosis (day 3) and all animal epidermal exposure sites showed erythema (day 10). The first challenge readings on day 24 showed no sensitization response. On day 25, 6 of 10 animals showed skin scaliness with two of those animals also showing minimal skim erythema. At the second challenge on days 31-32, 7 of 10 animals showed skin scaliness with minimal skin erythema scores. Skin irritation and inflammation increase the rate of skin turnover leading to scale formation. It is not surprising that the application of a severely irritating substance caused skin cell turnover and skin scaliness. However, this should not be considered a sign of skin sensitization.

It is interesting to note that a structurally similar and severely irritating peroxide, methyl isobutyl ketone peroxide, caused very similar skin necrosis, eryrthema and skin scaliness in a skin sensitization study (NOTOX project 245249). At a 0.5% concentration, 3 of 10 animals showed skin scaliness and at challenge the test animal that showed the highest erythema score was the same animal that exhibited injuries in depth (maximum erythema score) during the induction phase. Again, it is questionable whether the test substance induced sensitization or whether the skin effects were primarily indicative of a severe skin irritant following repeat exposures.

> ***QUESTION*: Does EPA agree that the minor skin sensitization responses observed only at second challenge may at least in part be due to the strong irritative effects of the PMN chemical following repeated exposure?**

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With respect to the weight of the evidence (WOE), we propose that the following decision tree approach published by the European Chemicals Agency (ECHA, 2015) is reasonable to follow for the PMN peroxide:

QUESTION 1: Is the substance, based on conclusive data, a skin sensitizer (GHS category 1, 1A or 1B?
RESPONSE 1: YES*

QUESTION 2: Is the substance a diisocyanate?
RESPONSE 2: NO

QUESTION 3: Are there any structural alerts (such as acid anhydride, platinum salt, etc.)?
RESPONSE 3: NO

QUESTION 4: Based on expert judgment, are there any other good reasons to suppose a potential respiratory sensitization hazard (e.g., human data, animal data, QSAR, *in vitro* test methods, etc.)?
RESPONSE 4: NO

CONCLUSION: Do not consider the substance a respiratory sensitizer.

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*Note: we do not consider the one older GPMT test to be conclusive

Based on the use of this published, technical method, we conclude that the PMN peroxide is not a respiratory sensitizer.

<u>QUESTION</u>: Does EPA agree that the WoE approach presented here is reasonable and takes into account the current state of the knowledge of respiratory sensitization, and if not, what is EPA's WoE approach?

We note that the EPA review document sent from Ernest Falke to Gloria Odusote dated September 14, 2018 includes a brief summary of the SAT assessment for mutagenicity and carcinogenicity. The summary mentions a marginal concern for oncogenicity based on potential free radical formation. We would like to remind EPA staff that the issue of the potential oncogenicity of organic peroxides was addressed many years by the Organic Peroxide Producers Safety Division (OPPSD).

In consultation with EPA, the OPPSD commissioned Dr. Thomas Slaga (University of Texas) to perform a series of in vivo studies in Sencar mice to address this specific issue (Slaga, 2004). The results of Dr. Slaga's work showed that organic peroxides should not be considered oncogenic. This work was submitted to EPA and was published in the scientific literature.

EPA agreed with the conclusion of the Slaga work and removed organic peroxides from the list of substances potentially thought to be oncogenic. The current chapter for peroxides in the U.S. EPA "TSCA New Chemicals Program (NCP) Chemicals Categories document (downloaded July 24, 2017 from the U.S. EPA website) states, "EPA has reviewed test data developed by the Society of the Plastics Industry (SPI) and others on the peroxide category of chemicals and concludes that available information does not support continued identification of peroxides as a new chemical category presenting concerns for possible carcinogenicity".

<u>QUESTION</u>: With no new information or rationale, why does EPA still have a concern for oncogenicity and include carcinogenicity in its SAT assessment of peroxides?

<u>Conclusions</u>

The PMN substance, as well as other similar peroxides, have been safely used for many years. EPA does not include respiratory sensitization as a health concern for peroxides in its NCP Chemical Categories document. The mechanism for skin and respiratory sensitization differ and therefore, a substance classified as a skin sensitizer should not automatically be considered a respiratory sensitizer. One animal laboratory skin sensitization study (and this test is only marginally positive) is not convincing evidence that the PMN substance is a skin sensitizer in humans. This view is consistently supported by the opinions of a number of recognized scientific experts in the field of sensitization as reported in the scientific literature. We are not aware of any scientific data that directly or indirectly supports the claim that the PMN substance is a respiratory sensitizer.

Therefore, we do not understand or agree with the suggested required use (and further confirmation of use) of a positive pressure facemask (APF 1000) with respect to the PMN chemical. The use of such significant PPE should be reserved for working conditions that present a high hazard level based on recognized human health concerns. To our opinion, there is no scientific basis for the selection of such PPE in this case.

AkzoNobel does not agree with or understand EPA's conclusion that the PMN substance is a respiratory sensitizer. We base this conclusion on 13+ years of safe use during the manufacture and industrial use of the substance (in Europe) with current industrial engineering controls and currently recommended respiratory protection.

AkzoNobel would like to meet with the EPA staff to further discuss the EPA conclusions with respect to the information presented in this document.

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ATTACHMENT 1
Toxicology Database Search Strategy

(1) Toxicology data search terms

=> QUE acute or ADME or allerg?
=> QUE cancer or carcinogen? or chronic? or cutaneous?
=> QUE damag? or dermal? or developm? or dose
=> QUE embryotox? or employe? or epidemiolog? or expose? or exposure or eye?
=> QUE fatal? or fertility or fetus or fetotox? or foetus or foetotox?
=> QUE gavage or genetic or genotox? or hazard? or kidney
=> QUE inhal? or intravenous or liver or guinea(w)pig(w)maximization or muta?
=> QUE neuro? or NOEL or NOAEL or ocular or pharmacokinetic?
=> QUE repeat(w)dose or respir? or reprod? or risk or safety or sensitiza? or skin or structure(w)activity or subchronic
=> QUE subcutaneous or target(w)organ or terat? or toxic? or threshold or worker

(2) Databases searched

Actor
https://actor.epa.gov/actor/home.xhtml

BG chemie
http://www.bgrci.de/webcom/show_article.php/_c-853/_cat-1/i.htm

GDCh, Gesellschaft Deutscher Chemiker
https://www.gdch.de/

JACC ECETOC European center for ecotoxicology and toxicology of chemicals
http://www.ecetoc.org/publications/jacc-reports/

OED The Global portal to Information on Chemical Substances
https://www.echemportal.org/echemportal/index?pageID=0&request_locale=en

ECHA European Chemicals Agency
https://echa.europa.eu/information-on-chemicals/registered-substances

SRC Fate Pointer

http://esc.syrres.com/fatepointer/search.asp

EPA DSSTox
https://www.epa.gov/chemical-research/distributed-structure-searchable-toxicity-dsstox-database

US EPA search
https://www.epa.gov/home/advanced-search

EPA TSCA Chemicals under Toxic Substances Control
https://www.epa.gov/chemicals-under-tsca

EPA High Production Volume,
https://ofmext.epa.gov/hpvis/HPVISlogon

EU Science Hub
https://ec.europa.eu/jrc/en

IARC International Agency for Research on Cancer
http://monographs.iarc.fr/

IPCS Inchem Chemical Safety Information from Intergovernmental Organizations
http://www.inchem.org/

JECDB Japan Existing Chemical Database
http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

NIST National Institute of Standards and Technology
https://www.nist.gov/

EPA New Chemicals Program
https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca

NIH National Institute of Environmental Health Sciences
https://www.niehs.nih.gov/health/

National Toxicology Program
https://ntp.niehs.nih.gov/

OECD Quantitative Structure Activity Relationship Project http://www.oecd.org/env/ehs/risk-assessment/oecdquantitativestructure-activityrelationshipsprojectqsars.htm#Download_the__QSARs_Application_Toolbox

Pubmed
https://www.ncbi.nlm.nih.gov/pubmed/

SER Social and Economic Council of the Netherlands
https://www.ser.nl/en/grenswaarden/1%20%20%20%204%20chloorfenoxy%20%201%20imidazol%201%20yl%203%20%203%20dimethyl%20%202%20butanon.aspx

TOXNET
https://toxnet.nlm.nih.gov/index.html

UK HSE Health and Safety Executive
http://www.hse.gov.uk/index.htm

WHO World health organization
http://www.who.int/ipcs/en/

IFA GESTIS International Limit values for chemical agents
http://www.dguv.de/ifa/gestis/gestis-internationale-grenzwerte-fuer-chemische-substanzen-limit-values-for-chemical-agents/index-2.jsp

EC SCOEL Scientific Committee on Occupational Exposure Limits
http://ec.europa.eu/social/main.jsp?catId=148&langId=en&intPageId=684

ATTACHMENT 2

Regulatory and code requirements limiting workplace exposures to monomers, organic peroxides, cobalt compounds, and other components of thermoset resin systems*

OSHA

• Under OSHA's Air Contaminants Standard (29 CFR 1910.1000), employers are required to use (in order of preference) source reduction, mechanical ventilation and/or respirators to limit workplace exposures to the styrene and/or methyl methacrylate that evaporates from resin (including gelcoat) systems. Controlling for these exposures effectively limits exposure to other substances that may be contained in resins.

- OSHA's 8-hour average Permissible Exposure Limit for is styrene 100 ppm and for methyl methacrylate is 100 ppm. Under the OSH Act's General Duty Clause, OSHA can also enforce compliance with the ACGIH TLVs for styrene (50ppm) and methyl methacrylate (50 ppm). See https://www.osha.gov/dsg/annotated-pels/tablez-1.html.

- The industry-recommended PEL for styrene is 20 ppm and for methyl methacrylate is 50 ppm. Many employers comply with these levels voluntarily. See http://styrene.org/wp-content/uploads/2016/05/10-24-11-Backgrounder-on-20ppmrecommendation. pdf and http://www.mpausa.org/methacrylates-and-respiratory/.
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• OSHA's standard for Spray Finishing Using Flammable and Combustible Materials (29 CFR 1910.107) requires that all spray application of thermoset resin take place in an area provided with mechanical ventilation meeting certain performance requirements.

• OSHA's Respiratory Protection Standard (29 CFR 1910.134) requires certain practices to ensure proper use of respirators.

EPA

• EPA's National Emission Standard for Hazards Air Pollutants: Reinforced Plastics Composites Production (40 CFR 63 Subpart WWWW) requires that resin spray operations meet certain emission limits using a combination of low-monomer resin and low-atomized spray technologies, both of which have the effect of reducing workplace exposures to styrene and methyl methacrylate. The low-atomized spray technologies will also reduce employee exposures to other substances contained in resins.

• Low-atomized spray technologies are also required under several state and local rules implemented to satisfy EPA's ambient air quality standards. See for example, South Coast (Los Angeles) Air Quality Management District's Rule 1132 and Rule 1162, at http://www.aqmd.gov/home/regulations/rules/scaqmd-rule-book/regulation-xi.

Fire Codes

• The National Fire Protections Association's Standard for Spray Application Using Flammable and Combustible Materials (NFPA 33) requires that areas where resin spray processes occur be provided with mechanical ventilation meeting certain performance requirements.

* Provided by the American Composites Manufacturers Association

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